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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,792	11/10/2005	Giuseppe Pier Pelicci	LEDER-0014	4653

23599 7590 05/01/2008

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ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
05/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,792	PELICCI ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *12-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/30/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-23 are all the pending claims for this application.

2. The preliminary amendment to the specification of 11/10/05 has been considered and entered.

3. Applicants amendment to bring the "use" claims from the claim set of 3/30/05 into statutory compliance under 35 U.S.C. 101 by amending the claims to a tumor classification method is acknowledged.

Election/Restrictions

4. Applicant's election with traverse of Group I (Claims 1-11) as to Group III (amended Claims 20-23) in the reply filed on 2/6/08 is acknowledged. The traversal is on the ground(s) that the elected groups possess unity of invention. A method for determining whether a treatment of a disorder with an HDAC inhibitor is to be started/continued or not and the classification scheme based thereon are overlapping subject matter and would not be an undue search burden.

Applicants' argument that the subject matter of Group I and Group III is overlapping is found persuasive in view of the amendment of Claim 11 to recite a tumor classifying method involving determining the histone acetylation levels in order determine whether to treat the tumor with an HDAC inhibitor and the amendment of Claims 20-23 (Group III) to depend from the method of Claim 11. The restriction of Group III is withdrawn.

Applicants' argument that searching the groups would not be an undue burden is irrelevant. This is not found persuasive because Applicants are reminded that an Examiner is not required to establish a search burden in finding lack of unity much less where a lack of unity restriction is required. Chapter 1800 of the MPEP does not speak to this issue.

5. Claims 12-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/6/08.

6. Applicant's election with traverse of species for a "condition associated with abnormal gene expression" (Claim 6) and a "colon and colorectal cancer" (Claim 7) in the reply filed on 2/6/08 is acknowledged. Applicants have not provided technical or legal arguments why the speciation of the invention is improper. Under 37 CFR 1.141, an allowed generic claim may link a reasonable number of species embraced thereby.

The practice is stated in 37 CFR 1.146 as follows:

37 CFR 1.146. Election of Species.

> In the first action on an application containing a generic claim to a generic invention (genus) and claims to more than one patentably distinct species embraced thereby, the examiner may require the applicant in the reply to that action to elect a species of his or her invention to which his or her claim will be restricted if no claim to the genus is found to be allowable. However, if such application contains claims directed to more than a reasonable number of species, the examiner may require restriction of the claims to not more than a reasonable number of species before taking further action in the application.

Accordingly, as stated at page 8 of the Office action of 11/21/07:

> Upon the allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, Applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

A different search would have to be performed to examine the claims to the extent that the claims are directed to a different type of disorder. Once again, upon the allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141.

The election of species requirement is deemed proper and therefore made FINAL for Claim 6. Thus the non-elected species are withdrawn from examination.

The election of species requirement for Claim 7 is withdrawn.

7. Claims 1-11 and 20-23 are all the pending claims under examination.

Information Disclosure Statement

8. Copies of the foreign patent documents have not been received therefore reference nos. 001 and 002 have been stricken on the 1449 from IDS from 3/30/05. The non-patent literature references cited in the IDS of 3/30/05 have been considered and entered with the exception for the entry under ref. #6 which has been stricken from the 1449 form. Applicants are invited to provide a copy of the document referred to by the URL or relevant portions.

Oath/Declaration

9. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It was not properly executed in accordance with either 37 CFR 1.66 or 1.68. The inventors listed as 201-203 and 205-207 on the oath/declaration of 11/10/05 have not properly executed the document because they have not provided the date of execution.

Specification

10. The specification is objected to because it does not cross-reference the related applications and their dates of filing.

Claim Objections

11. Claim 7 is objected to for the apparent misspelling of "testosterone" which should be amended to "testosterone."

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-11 and 20-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-10 are indefinite for the recitation "a treatment with an HDAC inhibitor is to be started/continued or not" because the intended meaning of the phrase "started/continued or not" is not clear. Is the intended endpoint for starting treatment, continuing treatment and/or discontinuing treatment based on the level of histone acetylation?

b) Claims 1-11 and 20-23 are indefinite for the recitation "a sample derived from tissue" in Claims 1 and 9-11 because the term "derived" is not clear within the meaning

of processing the sample for determining histone acetylation. The term "derived" has an art-recognized meaning as taking a material through a process in order to change a character (see attached Merriam-Webster on-line definition of "derived"). In order to examine the level of histone acetylation in a sample, would one of skill in the art need to process the material in some way in order to, for example, expose antigenic determinants for antibody binding?

c) Claims 1-7, 9-11 and 20-23 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the relationship between step a) of Claims 1 and 11, respectively and step b) of Claims 1 and 11, respectively. Is the histone acetylation level directly correlated with the extent of the antibody binding to the sample in the contacting step of b) or is the antibody used to immunopurify the acetylated histone which level is then quantitated by some other means?

d) Claim 10 is indefinite for the recitation "a further sample derived from tissue affected by the disorder which has been contacted with an HDAC inhibitor" because it is not clear from which individual the reference sample is obtained. Is the reference sample obtained from the same individual as the sample in step a) of Claim 1 or can it be from a different individual having the same disorder but who is being treated with an HDAC inhibitor or both.

Further it is not clear when the reference sample has been contacted with the HDAC inhibitor. Does this mean that the reference sample is taken from an individual

having been treated with the HDAC inhibitor so that the tissue would have already been exposed to and contacted by the inhibitor in vivo or that the sample once obtained from the tissue has been contacted with the inhibitor in vitro?

Still further, it is not clear whether the HDAC inhibitor of Claim 10 is required to be the same or different from the HDAC inhibitor of Claim 1. Would one of skill in the art know how to correlate the acetylation levels for the inhibitor of Claim 1 to the intended inhibitor of Claim 1 assuming the inhibitors are different?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Biological Deposit

13. Claims 4 and 5 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (a) known and readily available to the public; (b) reproducible from the written description.

a. It is unclear if hybridoma cell lines which produce an antibody having the exact chemical identity of G2M-T25-H4ac and G2M-T52-ac are known and publicly available, or can be reproducibly isolated without undue experimentation. Applicants' specification identifies the DSMZ depository address for the two cell lines at pp. 8-9, restates the two deposits having been made with the DSMZ (pp. 12-13), and restates the DSMZ address

and the date of deposit (9/24/02) along with the accession nos., ACC2578 and ACC2579, respectively, on p. 18. Applicants' have also provided deposit receipts for each of the hybridoma cell lines filed on 3/30/05. However, no where in the application do Applicants make a certified declaration of assurances that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application.

Therefore, either a suitable deposit for patent purposes or a declaration of deposit assurances is suggested. Without a publicly available deposit of the above hybridoma cell linec, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event. It would require undue experimentation to reproduce the claimed antibody species G2M-T25-H4ac and G2M-T52-ac. Deposit of the hybridomas or a declaration of deposit assurances would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty ***and that all restrictions upon public access to the deposited material will be irrevocably***

removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing

the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Written Description/ New Matter

14. Claims 20-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 20-23 are interpreted as being drawn to "antibody T25" and "antibody T52" or a conjugate thereof which are antibodies (and conjugates thereof) that are not described in the original specification or claims, and raise a new matter issue.

As discussed under section 12 above, the specification discloses the G2M-T25-

H4ac and G2M-T52-ac Mabs but does not disclose a "T25" or "T52" antibody much less that the antibodies would be capable of binding to acetylated histone but not to deacetylated histone. Applicants are requested to identify by exact page, paragraph and line number where the antibodies are disclosed in the application.

In the absence of structural characteristics for the T25 antibody or the T52 antibody with binding specificity for acetylated histone; one of skill in the art would reasonably conclude that Applicant was not in possession of the claimed antibody inventions. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

15. Claims 1, 3, and 6-11 are rejected under 35 U.S.C. 102(a) as being anticipated by HEINZEL et al. (EP 02021228.8; filed 9/18/02; referred to as "EP '228").

Claims 1, 3 and 6-10 are interpreted as being drawn to a method for determining whether to start treatment, continue treatment and/or discontinue treatment for any disorder with an HDACi based on the level of histone acetylation in a sample derived from tissue affected by the disorder compared to the level in a reference sample where

the level is determined by binding of acetylated histone to *any* antibody specific to *any* acetylated histone and where a significantly lower level of acetylation in the sample allows one to classify the disorder as being eligible for treatment with the HDACi (Claim 1), where the antibody is monoclonal (Claim 3), where the disorder is a condition associated with abnormal gene expression (Claim 6), where the disorders are listed in Claim 7, where the level of acetylation is determined by flow cytometry, immunochemistry, ELISA and/or Western Blot (Claim 8), where the reference sample is obtained from a tissue from a healthy individual where the tissue corresponds to the tissue affected by the disorder (Claim 9) and where the reference sample is a sample obtained from a tissue affected by the disorder where the tissue has been contacted with the HDACi.

Claim 11 is interpreted as being drawn to a method for classifying a tumor by contacting a sample obtained from a tissue affected by the tumor with an antibody that binds any acetylated histone but not to deacetylated histone, determining the level of acetylation based on the antibody interaction and classifying the tumor as to whether it should be treated with an HDACI based on whether the level of acetylated histone is significantly lower than a reference sample.

EP '228 teaches recruitment of HDACs in gene regulation for cellular proliferation and differentiation, where hyperacetylation of N-terminal tails of histones H3 and H4 are correlated with gene activation and deacetylation can mediate transcriptional repression (pp. 3-4); HDAC inhibitors (HDACi) may be beneficial in the treatment of some cancers and there is a need to "identify a characteristic profile for successful candidates as

HDACi,...identify early on patients who will benefit from therapy with HDACi, and monitor patients during therapy (pp. 4-5), where using specific markers such as histone acetylation can be used for profiling a HDACi (p. 5; Figure 2; Example 1). EP '228 teaches measuring, for example, the acetylated histone level in a sample for determining whether a treatment of a disorder with an HDACi is to be started/continued or not (Claim 12), where the sample is derived from tissue affected by the disorder or from a tissue of an individual treated with ah HDACi, or from a corresponding tissue from a healthy individual (pp. 6, 10) where the disorder is associate with abnormal gene expression such as skin cancer melanoma, estrogen receptor-dependent and independent breast cancer, ovarian cancer, testosteron receptor-dependent and independent prostate cancer, renal cancer, colon and colorectal cancer, pancreatic cancer, bladder cancer, esophageal cancer, stomach cancer, genitourinary cancer, gastrointestinal cancer, uterine cancer, astrocytomas, gliomas, basal cancer and squameous cell carcinoma, sarcomas as Kaposi's sarcoma and osteosarcoma, head and neck cancer, small cell and non-small cell lung carcinoma, leukemia, lymphomas and other blood cell cancers, and or thyroid resistance syndrome (p. 6), where detecting the marker with an antibody can be accomplished by western blotting, ELISA, immunochemistry and/or flow cytometry (p. 8), and determining the amount of the marker in the sample and reference sample in parallel (p. 10).

In Example 1 (pp. 15-18) EP '228 teaches a method for testing samples taken from acute promyelocytic leukemic or healthy mice treated with a HDACi or control in order to measure histone acetylation levels using anti-acetylated histone H3 antibodies

by Western Blot and immunohistochenistry in order to determine the efficacy of the HDACi. Whole cell extracts from the spleens of healthy and cancerous mice were shown to have enhanced levels of histone acetylation shown by blotting technique after treatment with the HDACi. Immunohistochemistry analysis of HDACi-treated leukemic mice using the Mab against acetylated histones showed increased histone acetylation in HDACi-treated cells including leukemic blasts.

Based on the general teaching of EP '228 and Example 1 one of skill in the art would readily interpret the disclosed methods encompassing classifying the disorder (Claim 1) or the tumor (Claim 11) as to be treated with the HDACi when the level of acetylation was less than that of the reference sample. Thus the methods for determining whether to initiate treatment, continue treatment or discontinue treatment with an HDACi based on actelyated histone levels from a test sample in relation to a reference sample was anticipated by EP '228.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. Claims 1, 2, 6-9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Butler et al. (Clin. Can. Res. 7:962-970 (2001); cited in the IDS of 3/30/05; Butler I) in view of Marks et al. (Nature Reviews Cancer 1:194-202 (2001); cited in the IDS of 3/30/05).

The interpretation of Claims 1, 6-9 and 11 is discussed above. Claim 2 is drawn to the method of Claim 1 where the antibody binds acetylated human histone 4 and the level of human histone H4 acetylation is determined.

The claimed method was prima facie obvious at the time of the invention over Butler in view of Marks.

Butler describes methods of treating human prostate CWR22 xenograft tumors in mice with HDAC inhibitor, pyroxamide, where the excised tumor tissue sample is compared to vehicle control tumor tissue sample (reference), showed increased accumulated acetylation of histone by Western blot using polyclonal antibodies against acetylated histones H2A, H2B, H3 or H4 (p. 965, Col. 1, ¶ 3; Figure 6A; p. 966, Col. 2, ¶1). The antibodies of Butler recognize human histone H4 and are used to determine the level of acetylation of human histone H4 in the prostate cancer. The human prostate

tumor of Butler would have been associated with abnormal gene expression. The level of human histone H4 acetylation was used to correlate the treatment effect of the HDACi against the vehicle control where Butler I teaches "the accumulation of acetylated histones may serve as a biological marker for the activity of HDAC inhibitor" (p. 967, Col. 1). Butler does not explicitly disclose that the level of histone acetylation would correlate with dosing in clinical trials whereas Marks describes on p. 197, Col. 2, last ¶ the occurrence of histone acetylation after HDAC treatment in normal and tumor cells and accumulation of acetylated histone is a useful marker of HDAC biological activity and can be used to monitor dosing in clinical trials (p. 199, Col. 2, ¶3).

It would have been prima facie obvious to have created the method invention in view of Butler and Marks. Both references disclose the use of histone acetylation as a marker for determining responsiveness to therapeutic agents, HDACi, in treating disorders, more especially prostate cancer. Both references disclose histone H3 and/or H4 as a preferred marker in assessing whether the extent of acetylation would correlate with tumor responsiveness to a drug, and that depending on the extent of acetylation, one could determine a clinical course of action, namely, monitoring the dose. Thus the combined method disclosures could have been considered by one of skill in the art as providing more than sufficient motivation to consider whether to start, continue or discontinue a treatment regimen for an HDAC inhibitor based on the level of human histone H3 or H4 acetylation using an antibody-based methods of screening. One skilled in the art would have been reasonably assured of success in creating the method invention because the reagents for screening histone acetylation were already in

existence and had already been shown to have specific binding activity in method assays for determining outcomes of HDACi therapy and continued course of treatment for specific disorders such as prostate cancer based on the combined reference disclosures of Butler and Marks. Butler and Marks rendered the claimed method invention prima facie obvious at the time of the invention.

17. Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being obvious over Heinzel et al. (EP 02021228.8; filed 9/18/02; referred to as "EP '228") in view of Butler et al. (Clin. Can. Res. 7:962-970 (2001); cited in the IDS of 3/30/05).

The interpretation of Claims 1 and 2 are discussed above.

The claimed method invention was prima facie obvious at the time of the invention over Heinzel, Butler and Ono.

The interpretation of Heinzel is discussed above. Heinzel appreciates screening histone acetylation in general and specifically H3 acetylation, but does not disclose using an antibody reagent that recognizes human histone H4 whereas Butler specifically provide for such a reagent in a relevant screening assay.

It would have been prima facie obvious to have created the method invention in view of Heinzel and Butler. Both references disclose the use of histone acetylation as a marker for determining responsiveness to therapeutic agents, HDACi, in treating disorders, more especially those associated with abnormal gene expression including cancers. Both references disclose histone H3 as preferred marker in assessing whether the extent of acetylation would correlate with tumor responsiveness to a drug, and that

depending on the extent of acetylation, one could determine a clinical course of action. One skilled in the art could have readily modified the method of Heinzel with the anti-human histone H4 antibody of Butler in order to measure the level of human histone H4 because Butler taught that H4 was a relevant marker for assessing therapeutic value of HDAC in vivo and that the extent of acetylation was directly correlative with tumor responsiveness to the drug. One skilled in the art would have been reasonably assured of success in having made the substitution of an H3 antibody for an H4 antibody because the reagents were available and had already been shown to be of use in a similarly applied assay system. Thus Heinzel and Butler rendered the claimed method invention prima facie obvious at the time of the invention.

Conclusion

19. No claims are allowed.

20. Reference(s) considered relevant to the general field but not relied on by the examiner:

Ono et al. (J. Exp. Clin. Can. Res. 21(3):377-382 (Sep 2002); Abstract).

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Examiner, Art Unit 1643
Temporary Signatory Authority